Clinical trial results:
Phase II, randomized, controlled, clinical trial exploring efficacy and safety of ERY001 (L-asparaginase encapsulated in Red Blood Cells) in combination with gemcitabine or FOLFOX regimen in second-line therapy for patients with progressive metastatic pancreatic carcinoma.

Summary

EudraCT number	2013-004262-34
Trial protocol	FR
Global end of trial date	07 November 2017

Results information

Result version number	v1 (current)
This version publication date	09 February 2022
First version publication date	09 February 2022

Trial information

Trial identification

Sponsor protocol code	GRASPANC 2013-03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02195180
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Erytech Pharma
Sponsor organisation address	60 Avenue Rockefeller, Lyon, France, 69008
Public contact	Anu Gupta, ERYTECH Pharma, +1650 5634176, anu.gupta@erytech.com
Scientific contact	Iman El-Hariry, ERYTECH Pharma, +1617 9592131, iman.elhariry@erytech.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 December 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The two co- primary objectives of the study were:
- To evaluate of the effects of eryaspase in terms of progression-free survival (PFS) when eryaspase is combined with chemotherapy for the second-line treatment of patients with pancreatic adenocarcinoma (PAC) whose tumors have low or no asparagine synthetase (ASNS) expression (ASNS 0/1+).
- To evaluate of the effects of eryaspase in terms of overall survival (OS) when eryaspase is combined with chemotherapy for the second-line treatment of patients with PAC whose tumors have low or no ASNS expression (ASNS 0/1+).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

An independent DSMB reviewed the interim results from the study as well as safety on a regular basis.

Background therapy:

Based on systematic reviews and NCCN guidelines, gemcitabine-based therapy can be given to those previously treated with fluoropyrimidine-based chemotherapy (Tempero 2017). Fluoropyrimidine-based chemotherapy regimens are acceptable second-line options for patients who have received prior gemcitabine-based therapy. Therefore, the choice of chemotherapy as the backbone of treatment in both treatment arms was justified.

Evidence for comparator: -

Actual start date of recruitment	31 March 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 141
Worldwide total number of subjects	141
EEA total number of subjects	141

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	81
From 65 to 84 years	60
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 141 adult patients were randomized 2:1 ratio to two arms: Eryaspase + Chemotherapy and Chemotherapy alone, and of those, 137 patients received treatment.

Pre-assignment

Screening details:

- Advanced or metastatic exocrine pancreatic adenocarcinoma.
- Only one 1 prior systemic therapy for advanced or metastatic disease. Progressed through first line.
- Age 18 years or older.
- Measurable lesion (>1 cm) as assessed by CT scan or MRI (RECIST criteria Version 1.1).
- ECOG PS of 0 or 1.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Eryaspase + chemotherapy

Arm description:

This arm received eryaspase at 100 U/kg combined with either gemcitabine or modified FOLFOX 6 regimen (mFOLFOX6, as plan protocol amendment-1 (26th Feb 2016) in second-line therapy of patients with progressive metastatic pancreatic adenocarcinoma. Choice of chemotherapy in second-line treatment was determined, depending on the chemotherapy used in the first-line. If the first-line regimen was FOLFIRINOX or a FOLFOX regime, the gemcitabine-based regimen was used. If the first-line was a gemcitabine-based regimen, FOLFIRINOX or a FOLFOX regime was used. Chemotherapy part was planned for a total of 6 cycles. However, the number of cycles was dependent on the patient's response/tolerance.

Arm type	Experimental
Investigational medicinal product name	Eryaspase
Investigational medicinal product code	
Other name	ERY001, GRASPA
Pharmaceutical forms	Dispersion for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Eryaspase was administered every 2 weeks at a dose of 100 U/kg for each administration. Two administrations of eryaspase alone were planned per course of chemotherapy. Each administration was done on the third day (D3) of the first week and the third day (D17) of the third week of each chemotherapy course. Eryaspase administrations continued as long as there was no specific limiting toxicity related to investigational product.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine regimen consisted of 1000 mg/m², 30 min i.v perfusion at D1 weekly for 3 out of 4 weeks. A period of 4 weeks constituted a full course/cycle of chemotherapy.

Investigational medicinal product name	mFOLFOX6
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Infusion
Routes of administration	Intravenous use, Intravenous bolus use

Dosage and administration details:

mFOLFOX6 was administered as followed (Allegra 2011): intravenous (i.v.) oxaliplatin 85 mg/m2 on D1 or D15, i.v. leucovorin at a dose of 400 mg/m² or levo-leucovorin at a dose of 200 mg/m2 on D1 or D15, and i.v. bolus 5-FU at a dose of 400 mg/m2 and continuous intravenous infusion (c.v.i.) 5-FU at a dose of 2400 mg/m2 on D1 and D2 or D15 and D16. The treatment was repeated every 2 weeks. Two consecutive period of 2 weeks (total of 4 weeks) constituted a full course/cycle of chemotherapy.

Arm title	Chemotherapy alone

Arm description:

Chemotherapy alone (without study treatment eryaspase) was planned for a total of 6 cycles. However, the number of cycles was dependent on the patient's response/tolerance. Patients received successive courses of chemotherapy according to investigator decision (gemcitabine or mFOLFOX6). The modified FOLFOX 6 regimen (mFOLFOX6, as plan protocol amendment-1 (26th Feb 2016) in second-line therapy of patients with progressive metastatic pancreatic adenocarcinoma. Choice of chemotherapy in second-line treatment was determined, depending on the chemotherapy used in the first-line. If the first-line regimen was FOLFIRINOX or a FOLFOX regime, the gemcitabine-based regimen was used. If the first-line was a gemcitabine-based regimen, FOLFIRINOX or a FOLFOX regime was used. Chemotherapy part was planned for a total of 6 cycles. However, the number of cycles was dependent on the patient's response/tolerance.

Arm type	Active comparator
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine regimen consisted in 1000 mg/m², 30 min i.v perfusion at D1 weekly for 3 out of 4 weeks. A period of 4 weeks constituted a full course/cycle of chemotherapy.

Investigational medicinal product name	mFOLFOX6
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

mFOLFOX6 was administered as followed (Allegra 2011): intravenous (i.v.) oxaliplatin 85 mg/m2 on D1 or D15, i.v. leucovorin at a dose of 400 mg/m² or levo-leucovorin at a dose of 200 mg/m2, and i.v. bolus 5-FU at a dose of 400 mg/m2 and continuous intravenous infusion (c.v.i.) 5-FU at a dose of 2400 mg/m2 on D1 and D2 or D15 and D16. The treatment was repeated every 2 weeks. Two consecutive period of 2 weeks (total of 4 weeks) constituted a full course/cycle of chemotherapy.

Number of subjects in period 1	Eryaspase + chemotherapy	Chemotherapy alone
Started	95	46
Completed	90	43
Not completed	5	3
Consent withdrawn by subject	3	2
health deterioration	2	-
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Eryaspase + chemotherapy

Reporting group description:

This arm received eryaspase at 100 U/kg combined with either gemcitabine or modified FOLFOX 6 regimen (mFOLFOX6, as plan protocol amendment-1 (26th Feb 2016) in second-line therapy of patients with progressive metastatic pancreatic adenocarcinoma. Choice of chemotherapy in second-line treatment was determined, depending on the chemotherapy used in the first-line. If the first-line regimen was FOLFIRINOX or a FOLFOX regime, the gemcitabine-based regimen was used. If the first-line was a gemcitabine-based regimen, FOLFIRINOX or a FOLFOX regime was used. Chemotherapy part was planned for a total of 6 cycles. However, the number of cycles was dependent on the patient's response/tolerance.

Reporting group title	Chemotherapy alone

Reporting group description:

Chemotherapy alone (without study treatment eryaspase) was planned for a total of 6 cycles. However, the number of cycles was dependent on the patient's response/tolerance. Patients received successive courses of chemotherapy according to investigator decision (gemcitabine or mFOLFOX6). The modified FOLFOX 6 regimen (mFOLFOX6, as plan protocol amendment-1 (26th Feb 2016) in second-line therapy of patients with progressive metastatic pancreatic adenocarcinoma. Choice of chemotherapy in second-line treatment was determined, depending on the chemotherapy used in the first-line. If the first-line regimen was FOLFIRINOX or a FOLFOX regime, the gemcitabine-based regimen was used. If the first-line was a gemcitabine-based regimen, FOLFIRINOX or a FOLFOX regime was used. Chemotherapy part was planned for a total of 6 cycles. However, the number of cycles was dependent on the patient's response/tolerance.

Reporting group values	Eryaspase + chemotherapy	Chemotherapy alone	Total
Number of subjects	95	46	141
Age categorical			
Adults (18 years or older)			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
<65 years	52	29	81
>65 years	43	17	60
Gender categorical			
Units: Subjects			
Female	42	16	58
Male	53	30	83
ECOG Status			
Eastern Cooperative Oncology Group (ECOG) performance status (PS) was evaluated (0 or 1)			
Units: Subjects			
ECOG PS 0	30	12	42
ECOG PS 1	65	34	99

Subject analysis sets

Subject analysis set title	Intend-to-treat (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population comprised all patients who were randomized to study treatment, regardless of whether they received study medication.

Subject analysis set title	Per Protocol (PP)
Subject analysis set type	Per protocol

Subject analysis set description:

The PP population included all patients in the ITT population who received at least 1 dose of study medication and who met all of the following criteria:

- Had no major deviation in inclusion/exclusion criteria.
- Had at least 1radiological assessment post-baseline.

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population is defined as all patients who received at least one dose of study drug.

Subject analysis set title	ITT, ASNS 0/1
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subset of the ITT analysis set with ASNS 0/1 expressing tumours

Subject analysis set title	PP, ASNS 0/1
Subject analysis set type	Per protocol

Subject analysis set description:

Subset of PP analysis set with ASNS 0/1 expressing tumours

Subject analysis set title	ITT ASNS 2+/3+
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population of patients with ASNS status 2+ ot 3+ is defined as all patients randomized.

Subject analysis set title	PP ASNS 2+/3+
Subject analysis set type	Per protocol

Subject analysis set description:

The per protocol population of patients with ASNS status of 2+ or 3+. It is defined as all patients in the ITT set who receive at least one dose of study medication and who meet all of the following criteria: Satisfy the Inclusion/exclusion criteria; Correct treatment group allocation according to randomization; No additional prohibited chemotherapy during the treatment phase; No prohibited concomitant medications. Major protocol violations leading to treatment or study discontinuation would exclude patients from the per protocol population.

Reporting group values	Intend-to-treat (ITT)	Per Protocol (PP)	Safety population
Number of subjects	141	135	137
Age categorical			
Adults (18 years or older)			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0

From 65-84 years	0	0	0
85 years and over	0	0	0
<65 years	81	77	78
>65 years	60	58	59
Gender categorical Units: Subjects			
Female	58	56	57
Male	83	79	80
ECOG Status			
Eastern Cooperative Oncology Group (ECOG) performance status (PS) was evaluated (0 or 1)			
Units: Subjects			
ECOG PS 0	42	40	40
ECOG PS 1	99	95	97

Reporting group values	ITT, ASNS 0/1	PP, ASNS 0/1	ITT ASNS 2+/3+
Number of subjects	98	95	43
Age categorical			
Adults (18 years or older)			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
<65 years	53	51	28
>65 years	45	44	15
Gender categorical Units: Subjects			
Female	43	42	15
Male	55	53	28
ECOG Status			
Eastern Cooperative Oncology Group (ECOG) performance status (PS) was evaluated (0 or 1)			
Units: Subjects			
ECOG PS 0	27	26	15
ECOG PS 1	71	69	27

Reporting group values	PP ASNS 2+/3+		
Number of subjects	40		
Age categorical			
Adults (18 years or older)			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		

Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
<65 years	26		
>65 years	14		
Gender categorical Units: Subjects			
Female	14		
Male	26		
ECOG Status			
Eastern Cooperative Oncology Group (ECOG) performance status (PS) was evaluated (0 or 1)			
Units: Subjects			
ECOG PS 0	14		
ECOG PS 1	26		

End points

End points reporting groups

Reporting group title	Eryaspase + chemotherapy

Reporting group description:

This arm received eryaspase at 100 U/kg combined with either gemcitabine or modified FOLFOX 6 regimen (mFOLFOX6, as plan protocol amendment-1 (26th Feb 2016) in second-line therapy of patients with progressive metastatic pancreatic adenocarcinoma. Choice of chemotherapy in second-line treatment was determined, depending on the chemotherapy used in the first-line. If the first-line regimen was FOLFIRINOX or a FOLFOX regime, the gemcitabine-based regimen was used. If the first-line was a gemcitabine-based regimen, FOLFIRINOX or a FOLFOX regime was used. Chemotherapy part was planned for a total of 6 cycles. However, the number of cycles was dependent on the patient's response/tolerance.

Reporting group title	Chemotherapy alone

Reporting group description:

Chemotherapy alone (without study treatment eryaspase) was planned for a total of 6 cycles. However, the number of cycles was dependent on the patient's response/tolerance. Patients received successive courses of chemotherapy according to investigator decision (gemcitabine or mFOLFOX6). The modified FOLFOX 6 regimen (mFOLFOX6, as plan protocol amendment-1 (26th Feb 2016) in second-line therapy of patients with progressive metastatic pancreatic adenocarcinoma. Choice of chemotherapy in second-line treatment was determined, depending on the chemotherapy used in the first-line. If the first-line regimen was FOLFIRINOX or a FOLFOX regime, the gemcitabine-based regimen was used. If the first-line was a gemcitabine-based regimen, FOLFIRINOX or a FOLFOX regime was used. Chemotherapy part was planned for a total of 6 cycles. However, the number of cycles was dependent on the patient's response/tolerance.

Subject analysis set title	Intend-to-treat (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population comprised all patients who were randomized to study treatment, regardless of whether they received study medication.

Subject analysis set title	Per Protocol (PP)
Subject analysis set type	Per protocol

Subject analysis set description:

The PP population included all patients in the ITT population who received at least 1 dose of study medication and who met all of the following criteria:

- Had no major deviation in inclusion/exclusion criteria.
- Had at least 1radiological assessment post-baseline.

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population is defined as all patients who received at least one dose of study drug.

Subject analysis set title	ITT, ASNS 0/1
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subset of the ITT analysis set with ASNS 0/1 expressing tumours

Subject analysis set title	PP, ASNS 0/1
Subject analysis set type	Per protocol

Subject analysis set description:

Subset of PP analysis set with ASNS 0/1 expressing tumours

Subject analysis set title	ITT ASNS 2+/3+
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population of patients with ASNS status 2+ ot 3+ is defined as all patients randomized.

Subject analysis set title	PP ASNS 2+/3+
Subject analysis set type	Per protocol

Subject analysis set description:

The per protocol population of patients with ASNS status of 2+ or 3+. It is defined as all patients in the ITT set who receive at least one dose of study medication and who meet all of the following criteria: Satisfy the Inclusion/exclusion criteria; Correct treatment group allocation according to randomization; No additional prohibited chemotherapy during the treatment phase; No prohibited concomitant medications. Major protocol violations leading to treatment or study discontinuation would exclude patients from the per protocol population.

Primary: Progression-free survival (PFS), ASNS 0/1

End point title	Progression-free survival (PFS), ASNS 0/1

End point description:

PFS defined as the time elapsed between randomisation and death from any cause or progression. For any patients who had not progressed or died at the time of database lock, PFS was censored at the date of last radiological assessment prior to database lock.

End point type	Primary

End point timeframe:

Complete study period

End point values	Eryaspase + chemotherapy	Chemotherapy alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	29		
Units: months				
median (confidence interval 95%)	2.1 (1.7 to 3.4)	2.5 (1.4 to 3.4)		

Statistical analyses

Statistical analysis title	PFS, ASNS 0/1

Statistical analysis description:

Stratified log-rank test, with the stratification variable being the type of chemotherapy treatment (gemcitabine or mFOLFOX6).

Comparison groups	Eryaspase + chemotherapy v Chemotherapy alone
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.124 [1]
Method	Stratified logrank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1.12

Notes:

[1] - Not statistically significant different for PFS in the ASNS 0/1 subgroup

Primary: Overall survival (OS), ASNS 0/1

End point title	Overall survival (OS), ASNS 0/1

End point description:

OS defined as the time elapsed between randomisation and death from any cause. For any patients who had not died at the time of database lock, OS was censored at the date of last contact before database lock.

End point type	Primary

End point timeframe:

Complete study period

End point values	Eryaspase + chemotherapy	Chemotherapy alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	32		
Units: months				
median (confidence interval 95%)	6.2 (5.1 to 8.8)	4.9 (3.1 to 7.1)		

Statistical analyses

Statistical analysis title	OS, ASNS 0/1

Statistical analysis description:

Stratified log-rank test, with the stratification variable being the type of chemotherapy treatment (gemcitabine or mFOLFOX6).

Comparison groups	Eryaspase + chemotherapy v Chemotherapy alone
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.054 [2]
Method	Stratified logrank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	1.01

Notes:

[2] - Approaching statistical significance at the 5% level. Weak evidence supporting differences for OS in the ASNS 0/1 subgroup

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

PFS in ITT analysis set

End point type	Secondary

End point timeframe:

Complete study period

End point values	Eryaspase + chemotherapy	Chemotherapy alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	46		
Units: months				
median (confidence interval 95%)	2.1 (1.8 to 3.4)	1.6 (1.3 to 3.0)		

Statistical analyses

Statistical analysis title	PFS, ITT
Comparison groups	Eryaspase + chemotherapy v Chemotherapy alone
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005 [3]
Method	Stratified logrank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	0.84

Notes:

[3] - Statistically significant differences for PFS in the ITT analysis set

Secondary: Overall survival (OS)

End point title	Overall survival (OS)
End point description: OS in ITT analysis set	
End point type	Secondary
End point timeframe: Complete study period	

End point values	Eryaspase + chemotherapy	Chemotherapy alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	46		
Units: months				
median (confidence interval 95%)	6.0 (4.8 to 6.6)	4.4 (3.0 to 5.0)		

Statistical analyses

Statistical analysis title	OS, ITT
Comparison groups	Eryaspase + chemotherapy v Chemotherapy alone
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007 [4]
Method	Stratified logrank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	0.87

Notes:

[4] - Statistically significant differences for OS in ITT analysis set

Secondary: Objective response

End point title	Objective response

End point description:

Objective response was defined as tumour response (complete response [CR] or partial response [PR]) per modified RECIST V1.1.

End point type	Secondary

End point timeframe:

Complete study period

End point values	Eryaspase + chemotherapy	Chemotherapy alone	Intend-to-treat (ITT)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	95	46	141	
Units: binary	9	4	13	

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control

End point title	Disease control

End point description:

Disease control was defined as CR, PR, or stable disease for at least 16 weeks, as determined by modified RECIST V1.1.

End point type	Secondary

End point timeframe:

Complete study period

End point values	Eryaspase + chemotherapy	Chemotherapy alone	Intend-to-treat (ITT)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	95	46	141	
Units: binary	46	11	57	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first trial-related activity after the patient had signed the ICF until 4 weeks after the last administration of study drug.

Adverse event reporting additional description:

All adverse events (AE) were followed until resolution or until 4 weeks after the last administration of study treatment. Serious adverse events (SAEs) were recorded throughout the study duration and followed until the subject has recovered, stabilized, recovered with sequelae or died. Adverse events were assessed at each visit and recorded in eCRF

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Eryaspase + Chemotherapy

Reporting group description:

Safety population

Reporting group title	Chemotherapy alone

Reporting group description:

Safety population

Serious adverse events	Eryaspase + Chemotherapy	Chemotherapy alone	
Total subjects affected by serious adverse events			
subjects affected / exposed	42 / 93 (45.16%)	22 / 44 (50.00%)	
number of deaths (all causes)	10	8	
number of deaths resulting from adverse events	10	8	
Vascular disorders			
Jugular vein thrombosis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	7 / 93 (7.53%)	4 / 44 (9.09%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 4	0 / 4	
Asthenia			
subjects affected / exposed	1 / 93 (1.08%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	4 / 93 (4.30%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	0 / 93 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Generalised oedema			
subjects affected / exposed	0 / 93 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia			
subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 93 (1.08%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	

Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	2 / 93 (2.15%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 93 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device occlusion			
subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis in device			

subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Antibody test positive			
subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Transfusion reaction			
subjects affected / exposed	3 / 93 (3.23%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 93 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular disorder			
subjects affected / exposed	0 / 93 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
coma			
subjects affected / exposed	0 / 93 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 93 (1.08%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 93 (1.08%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 93 (4.30%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 93 (2.15%)	3 / 44 (6.82%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	4 / 93 (4.30%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 93 (1.08%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vomiting			
subjects affected / exposed	2 / 93 (2.15%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Constipation			
subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal stenosis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric vein thrombosis			
subjects affected / exposed	0 / 93 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	3 / 93 (3.23%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bile duct stenosis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			

subjects affected / exposed	2 / 93 (2.15%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis acute			
subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 93 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 93 (1.08%)	2 / 44 (4.55%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	2 / 93 (2.15%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bronchitis			
subjects affected / exposed	0 / 93 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia klebsiella			
subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis septic			
subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			

subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 93 (1.08%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 93 (1.08%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Eryaspase + Chemotherapy	Chemotherapy alone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	93 / 93 (100.00%)	44 / 44 (100.00%)	
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	18 / 93 (19.35%)	11 / 44 (25.00%)	
occurrences (all)	27	14	
Weight decreased			
subjects affected / exposed	15 / 93 (16.13%)	9 / 44 (20.45%)	
occurrences (all)	18	11	
Alloimmunisation			
subjects affected / exposed	15 / 93 (16.13%)	0 / 44 (0.00%)	
occurrences (all)	15	0	
Blood alkaline phosphatase increased			

subjects affected / exposed	8 / 93 (8.60%)	4 / 44 (9.09%)	
occurrences (all)	11	5	
Blood bilirubin increased			
subjects affected / exposed	8 / 93 (8.60%)	1 / 44 (2.27%)	
occurrences (all)	12	1	
Antithrombin III decreased			
subjects affected / exposed	7 / 93 (7.53%)	0 / 44 (0.00%)	
occurrences (all)	11	0	
Neutrophil count decreased			
subjects affected / exposed	6 / 93 (6.45%)	1 / 44 (2.27%)	
occurrences (all)	7	1	
Platelet count decreased			
subjects affected / exposed	5 / 93 (5.38%)	2 / 44 (4.55%)	
occurrences (all)	9	3	
Alanine aminotransferase increased			
subjects affected / exposed	14 / 93 (15.05%)	2 / 44 (4.55%)	
occurrences (all)	24	2	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	8 / 93 (8.60%)	4 / 44 (9.09%)	
occurrences (all)	10	4	
Headache			
subjects affected / exposed	9 / 93 (9.68%)	1 / 44 (2.27%)	
occurrences (all)	14	1	
Paraesthesia			
subjects affected / exposed	6 / 93 (6.45%)	4 / 44 (9.09%)	
occurrences (all)	7	4	
Neuropathy peripheral			
subjects affected / exposed	13 / 93 (13.98%)	9 / 44 (20.45%)	
occurrences (all)	28	14	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	63 / 93 (67.74%)	28 / 44 (63.64%)	
occurrences (all)	132	55	
Pyrexia			

subjects affected / exposed	27 / 93 (29.03%)	12 / 44 (27.27%)	
occurrences (all)	51	21	
General physical health deterioration			
subjects affected / exposed	13 / 93 (13.98%)	3 / 44 (6.82%)	
occurrences (all)	14	3	
Oedema peripheral			
subjects affected / exposed	16 / 93 (17.20%)	7 / 44 (15.91%)	
occurrences (all)	19	7	
Fatigue			
subjects affected / exposed	11 / 93 (11.83%)	7 / 44 (15.91%)	
occurrences (all)	40	26	
Mucosal inflammation			
subjects affected / exposed	11 / 93 (11.83%)	3 / 44 (6.82%)	
occurrences (all)	11	5	
Chills			
subjects affected / exposed	8 / 93 (8.60%)	0 / 44 (0.00%)	
occurrences (all)	12	0	
Oedema			
subjects affected / exposed	1 / 93 (1.08%)	1 / 44 (2.27%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	42 / 93 (45.16%)	23 / 44 (52.27%)	
occurrences (all)	100	52	
Thrombocytopenia			
subjects affected / exposed	40 / 93 (43.01%)	16 / 44 (36.36%)	
occurrences (all)	104	40	
Neutropenia			
subjects affected / exposed	23 / 93 (24.73%)	7 / 44 (15.91%)	
occurrences (all)	39	16	
Lymphopenia			
subjects affected / exposed	10 / 93 (10.75%)	3 / 44 (6.82%)	
occurrences (all)	17	6	
Gastrointestinal disorders			
Nausea			

subjects affected / exposed	58 / 93 (62.37%)	26 / 44 (59.09%)	
occurrences (all)	102	31	
Vomiting			
subjects affected / exposed	42 / 93 (45.16%)	15 / 44 (34.09%)	
occurrences (all)	73	23	
Abdominal pain			
subjects affected / exposed	34 / 93 (36.56%)	16 / 44 (36.36%)	
occurrences (all)	45	27	
Diarrhoea			
subjects affected / exposed	37 / 93 (39.78%)	13 / 44 (29.55%)	
occurrences (all)	66	15	
Constipation			
subjects affected / exposed	26 / 93 (27.96%)	12 / 44 (27.27%)	
occurrences (all)	30	17	
Abdominal pain upper			
subjects affected / exposed	14 / 93 (15.05%)	9 / 44 (20.45%)	
occurrences (all)	18	11	
Stomatitis			
subjects affected / exposed	15 / 93 (16.13%)	5 / 44 (11.36%)	
occurrences (all)	25	5	
Haemorrhoids			
subjects affected / exposed	8 / 93 (8.60%)	3 / 44 (6.82%)	
occurrences (all)	8	3	
Ascites			
subjects affected / exposed	6 / 93 (6.45%)	4 / 44 (9.09%)	
occurrences (all)	44	4	
Gastrooesophageal reflux disease			
subjects affected / exposed	7 / 93 (7.53%)	2 / 44 (4.55%)	
occurrences (all)	7	3	
Dry mouth			
subjects affected / exposed	3 / 93 (3.23%)	3 / 44 (6.82%)	
occurrences (all)	3	3	
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed	11 / 93 (11.83%)	3 / 44 (6.82%)	
occurrences (all)	15	4	
Dyspnoea			
subjects affected / exposed	9 / 93 (9.68%)	4 / 44 (9.09%)	
occurrences (all)	9	4	
Epistaxis			
subjects affected / exposed	8 / 93 (8.60%)	1 / 44 (2.27%)	
occurrences (all)	10	1	
Pulmonary embolism			
subjects affected / exposed	4 / 93 (4.30%)	1 / 44 (2.27%)	
occurrences (all)	4	1	
Productive cough			
subjects affected / exposed	2 / 93 (2.15%)	3 / 44 (6.82%)	
occurrences (all)	2	3	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	2 / 93 (2.15%)	1 / 44 (2.27%)	
occurrences (all)	3	1	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	11 / 93 (11.83%)	1 / 44 (2.27%)	
occurrences (all)	23	3	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	10 / 93 (10.75%)	6 / 44 (13.64%)	
occurrences (all)	11	6	
Insomnia			
subjects affected / exposed	8 / 93 (8.60%)	6 / 44 (13.64%)	
occurrences (all)	8	7	
Sleep disorder			
subjects affected / exposed	1 / 93 (1.08%)	2 / 44 (4.55%)	
occurrences (all)	1	2	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	12 / 93 (12.90%)	5 / 44 (11.36%)	
occurrences (all)	15	7	

Myalgia			
subjects affected / exposed	7 / 93 (7.53%)	3 / 44 (6.82%)	
occurrences (all)	8	3	
Arthralgia			
subjects affected / exposed	5 / 93 (5.38%)	2 / 44 (4.55%)	
occurrences (all)	9	4	
Pain in extremity			
subjects affected / exposed	5 / 93 (5.38%)	3 / 44 (6.82%)	
occurrences (all)	6	3	
Musculoskeletal pain			
subjects affected / exposed	6 / 93 (6.45%)	0 / 44 (0.00%)	
occurrences (all)	7	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 93 (3.23%)	2 / 44 (4.55%)	
occurrences (all)	3	2	
Urinary tract infection			
subjects affected / exposed	5 / 93 (5.38%)	0 / 44 (0.00%)	
occurrences (all)	6	0	
Sepsis			
subjects affected / exposed	0 / 93 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	29 / 93 (31.18%)	16 / 44 (36.36%)	
occurrences (all)	31	20	
Hypoalbuminaemia			
subjects affected / exposed	8 / 93 (8.60%)	8 / 44 (18.18%)	
occurrences (all)	13	8	
Hypokalaemia			
subjects affected / exposed	13 / 93 (13.98%)	3 / 44 (6.82%)	
occurrences (all)	24	4	
Hyperglycaemia			
subjects affected / exposed	11 / 93 (11.83%)	2 / 44 (4.55%)	
occurrences (all)	23	2	
Hyponatraemia			

subjects affected / exposed	6 / 93 (6.45%)	4 / 44 (9.09%)	
occurrences (all)	6	5	
Iron deficiency			
subjects affected / exposed	0 / 93 (0.00%)	3 / 44 (6.82%)	
occurrences (all)	0	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 February 2016	Main changes in Amendment 1 include: 1. Statistical considerations 1.1. Increase in number of patients enrolled in the study from 90 to ~133 taking into account that 40% PFS rate at 16 weeks in the ERY001 arm would be considered clinically meaningful for further investigation. 1.2. Update of study objectives and endpoints to align with clinical development plan for ERY001. 1.3. Clarification on study population definition included in the study. No addition data are needed related to update items 1.2 &1.3. 1.4. Overall safety follow-up at least 1year post administration 2. Safety 2.1. Update ERY001 safety information based on most recent experience with IMP. 2.2. Implementation of recommendations from the DSMB regarding the dose adjustment rules 3. PKPD assessment: 3.1. Removal of pharmacokinetic (asparaginase activity) and pharmacodynamic (asparagine depletion) 3.2. Change of laboratory facilities from CRS to SGS Cephac for amino-acid and asparaginase activity assays for the initial samples drawn 3.3. Possibility to perform PKPD and/or DNA collection after the end of the trial for research purpose. Complementary information for ongoing patients. 4. Other clarification / complementary Information: 4.1. Clarification that the name of FOLFOX regiment utilized in the study is mFOLFOX6 vs. FOLFOX4. The predefine regimen has not been modified 4.2. Study Termination clarification 4.3. ICF updated related to the PKPD removal 4.4. Language and/or typing errors improvement,

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported